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Caffeine improves endurance in 75-yr-old citizens: a randomized, double-blind, placebo-controlled, crossover study

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Norager, C. B., M. B. Jensen, M. R. Madsen, and S. Laurberg. Caffeine improves endurance in 75-yr-old citizens: a randomized, double-blind, placebo-controlled, crossover study. *J Appl Physiol* 99: 2302–2306, 2005. First published August 4, 2005; doi:10.1152/japplphysiol.00309.2005.—This study investigated the effect of caffeine on physical performance in healthy citizens aged ≥ 70 yr. The randomized, double-blind, placebo-controlled, crossover study was conducted in 15 men and 15 women recruited by their general practitioner. Participants abstained from caffeine for 48 h and were randomized to receive one capsule of placebo and then caffeine (6 mg/kg) or caffeine and then placebo with 1 wk in between. One hour after intervention, we measured reaction and movement times, postural stability, walking speed, cycling at 65% of expected maximal heart rate, perceived effort during cycling, maximal isometric arm flexion strength, and endurance. Analysis was by intention to treat, and $P < 0.05$ was regarded as significant. Caffeine increased cycling endurance by 25% [95% confidence interval (CI): 13–38; $P = 0.0001$] and isometric arm flexion endurance by 54% (95% CI: 29–83; $P = 0.0001$). Caffeine also reduced the rating of perceived exertion after 5 min of cycling by 11% (95% CI: 5–17; $P = 0.002$) and postural stability with eyes open by 25% (95% CI: 2–53; $P = 0.03$). Caffeine ingestion did not affect muscle strength, walking speed, reaction, and movement times. At the end of the study, 46% of participants correctly identified when they received caffeine and placebo. Caffeine increased exercise endurance in healthy citizens aged ≥ 70 yr, but the participants' reasons for stopping the test may have varied between subjects, as the cycling test was done at $\sim 55\%$ of maximal oxygen consumption. Further studies are required to investigate whether caffeine can be utilized to improve the physical performance of elderly citizens.

fatigue; perceived exertion; postural stability; elderly

CAFFEINE INGESTION INCREASES the endurance of young people exercising at 60–85% of their maximal oxygen uptake (12, 13, 38). It also seems to improve endurance as measured by repeated submaximal isometric contraction (34) and decreases the rate of perceived exertion during exercise (6, 9, 37). Typically, doses of ~ 6 mg/kg caffeine (equivalent to 4 cups of coffee) were used in these studies.

With a growing number of elderly with a physically active lifestyle and many elderly participating in rehabilitation programs, the endurance-enhancing effect of caffeine is of increasing interest in this age group. However, the endurance-enhancing effect of caffeine found in young subjects has not previously been examined in the elderly.

The aim of this study was to investigate whether 6 mg/kg caffeine improves physical performance and reduces the perceived effort during work in healthy citizens aged ≥ 70 yr. The

main hypothesis was that caffeine would improve cycling endurance at 65% of expected maximal heart rate, and the secondary hypothesis was that caffeine would improve postural stability, reaction and movement times, isometric arm flexion endurance, and walking speed and would reduce the rate of perceived exertion after 5 min of cycling in healthy elderly ≥ 70 yr.

MATERIALS AND METHODS

Participants. Healthy elderly individuals (15 men and 15 women), aged ≥ 70 yr, undergoing a physical examination for driver license renewal, were recruited by 15 general practitioners in Herning, Denmark, between July 2002 and October 2003. Exclusion criteria were dementia or invalidating psychiatric disease; general debility, angina, or other diseases that would render participation in the test program impossible; treatment with beta-receptor blocking drugs, calcium-channel blocking drugs, digitalis, or nitroglycerine; acute disease e.g., infection, and injury; diabetes; conditions that would contraindicate caffeine ingestion or participation in the test program; treatment with medication that interacts with caffeine, e.g., theophylline; and ingestion of caffeine-containing drinks and foods 48 h before each session.

Subjects with minor disabilities as hypertension treated with angiotensin I-converting enzyme inhibitors or diuretics, well-treated asthma, and slight osteoarthritis were considered suitable for inclusion.

In accordance with the Helsinki Declaration II, written, informed consent was obtained from all participants before study entry. The study was approved by the National Board of Health and the Regional Ethical Committee and was monitored by the Good Clinical Practice Unit at Aarhus University Hospital, Denmark.

Procedures. This randomized, double-blind, placebo-controlled, crossover study was carried out at the Surgical Research Unit, Herning Hospital, Denmark. All 30 subjects were examined twice, with a time interval of 1 wk between each session.

Randomization to placebo-caffeine or caffeine-placebo treatment was stratified by gender and carried out using sealed, numbered, opaque envelopes. The pharmacy department of Herning Hospital produced a white capsule containing 6 mg/kg caffeine (Unikem, Copenhagen, Denmark) and a placebo capsule (containing glucose monohydrate). On opening the randomization envelope, the pharmacy department packed the medication accordingly. Participants and investigators were unaware of treatment allocation at all times. Code-breaking sheets for emergency use were kept at the pharmacy department but were never used.

Participants avoided caffeine-containing drinks and food for 48 h before each visit. A diet rich in carbohydrates was recommended on the preceding day and up until 2 h before each session.

At each visit, a medical history was taken and physical examination performed, with body weight, height, blood pressure, heart rate, and

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an electrocardiogram recorded. Capsules were taken with a glass of water, and the subject then rested for 1 h. The following parameters were then measured: psychomotor function (reaction and movement times), postural stability, walking speed, cycling endurance at 65% of the expected maximal heart rate, and perceived effort during cycling. A carbohydrate-containing drink (150 ml) and a sandwich were then served. After a rest of 30 min, the maximal voluntary isometric arm flexion strength was measured. The subject then rested for an additional 15 min before endurance was recorded (when producing a force corresponding to 50% of the maximal isometric arm flexion strength). After each session, participants were asked if they had any symptoms during the caffeine-avoiding 48-h period (withdrawal symptoms) or through the examination period (side effects).

Endurance was measured on a cycle ergometer (Ergoline Ergometrics 900, Kivex, Denmark), with an increasing load of 25 W every second minute until 65% of the expected maximal heart rate (220 minus age) was reached. The load remained at this level, and the time until exhaustion was recorded. The rate of perceived exertion was measured after 5 min of cycling and at exhaustion using Borg's 20-point scale (2).

Psychomotor function was measured as reaction and movement time ("Good Response," Metitur, Jyväskylä, Finland) (8). Subjects sat in front of the response unit with their index finger on a "base" button. Reaction time was measured as the time between seeing a light signal and lifting the index finger from the base button. Movement time was measured as the time taken for the index finger to move from the base button to the light signal button. Subjects familiarized themselves with the program two to three times before the actual recording was made. Twelve measurements were taken for both reaction and movement times, and the mean values were calculated.

Postural stability was measured three times on a dynamometer platform ("Good Balance," Metitur) (31). Subjects stood on the platform with legs slightly apart and feet parallel to each other. Measurements were taken with eyes opened and closed (each for 30 s). Finally, a measurement was made for 20 s in the semitandem standing position (feet together and parallel, with the front of the posterior foot at the arch of the anterior foot). The velocity moment calculated as the mean area covered by the movement of the center of pressure during each second of the test was recorded.

Walking speed was measured over a distance of 15 m. Subjects walked the distance as fast as possible, and the best result of the two attempts was recorded.

The maximal voluntary isometric arm flexion strength was measured in the dominant arm using a strain gauge mounted on a dynamometer chair (Good Strength, Metitur) (7). The arm was flexed at 90° and held in a semiprone position (with the thumb pointing upward). Results were computerized, and the best result of three measurements was used.

Isometric endurance was measured with the person in the same position as during the maximal arm flexion strength testing. Subjects were asked to hold a force of 50% of their maximal strength. The isometric arm flexion endurance was measured as the time until this force could no longer be held.

At the end of the study, participants were asked to estimate the order in which they had received caffeine and placebo or to state if they detected no difference between the two capsules. Follow-up ended after completion of the last test session.

Data were entered before treatment codes were broken and analyzed on an intent-to-treat basis, according to a preestablished analysis plan.

Statistical analysis. The study was designed so that 30 evaluated participants would be sufficient to detect an 11% relative difference in cycling endurance with 80% certainty at the 5% level (assuming the SD of the difference to be 10%).

Data were \log_e transformed, and the distribution was evaluated graphically and by Shapiro-Wilk's test for normality. If data were

normally distributed, the two-sample *t*-test for unpaired data was used, otherwise the Mann-Whitney test for unpaired data was used.

Subjects received placebo and then caffeine (*group A*) or caffeine and then placebo (*group B*). To test for the presence of a treatment effect, the difference in response (*period 1* – *period 2*) was compared between *groups A* and *B* (1). The magnitude of the treatment effect was estimated as one-half of the difference in response for *group A* plus *group B*; consequently, the different treatment order was taken into account. To test for a possible period effect, the treatment responses in *group A* and *group B* were compared. To test for a possible treatment-period interaction, the means of both periods for the two groups were compared, and the differences visually analyzed (18).

Analyses were carried out using STATA software version 7.0 (StataCorp 2001, College Station, TX), and reported *P* values were based on the two-sided alternative hypothesis (with *P* < 0.05 regarded as being statistically significant).

RESULTS

Of 134 participants initially assessed for eligibility, 40 participants were included, and 30 were randomized. Eight subjects were excluded due to abnormal electrocardiogram, treatment with β -receptor-blocking drugs or calcium channel-blocking drugs, and ingestion of caffeine before session. Two subjects dropped out due to a stroke and an ill husband. Baseline values are summarized in Table 1. Two subjects were caffeine nonusers, and 28 subjects were users with a mean daily coffee intake of 4.9 cups of coffee, corresponding to ~486 mg caffeine daily.

For the primary endpoint of cycling endurance, all subjects worked at the same load in *periods 1* and *2*, except that two persons worked at 50 W during the placebo trial and 75 W during the caffeine trial. For both persons, the endurance was greater with the higher load in the caffeine period. We did not handle these two persons differently than the rest of the test persons in the statistical analysis. The median load was 50 W in both *groups A* and *B*. Caffeine produced a statistically significant increase in biking endurance from baseline (*P* < 0.0001). It increased endurance by 14% in *group A* and by 32% in *group B*; the difference between the two groups was statis-

Table 1. Subject characteristics

	Total
Men/women	15/15
Age,* yr	74.7 (5.5)
Height,* cm	164.3 (9.2)
Weight,* kg	72.1 (13.4)
Regular coffee intake,* cups/day	4.5 (3.3)
Physical activity† per week,* h	3.0 (2.6)
Withdrawal symptoms, no. (%)	
Total	15 (50)
Headache	11 (73)
Tiredness	7 (47)
Other symptoms‡	4 (27)
Side effects, no. (%)	
Total	14 (47)
Dizziness	6 (43)
Restlessness	6 (43)
Nausea	5 (36)
Other symptoms§	5 (36)

*Values are means (SD). †Cycling, walking, swimming, gymnastics. ‡Irritability, swollen legs, and soreness of muscles. §Headache, sense of heat, disturbance of vision, and heartburn.

tically significant ($P = 0.049$). The estimate of the effect of treatment in groups A and B, i.e., taking the order of treatment into account, was 25% [95% confidence interval (CI): 13–38; $P = 0.0001$]. A statistical test for treatment-period interaction was not significant ($P = 0.12$). Seven subjects in group A and two subjects in group B achieved an increase of >40% in endurance time with caffeine intake, but no outstanding characteristics could be found for these nine subjects: six men and three women, mean age 74.9 yr, mean daily coffee intake of 4.7 cups, and mean physical activity of 3 h weekly. For subjects drinking ≥ 6 cups of coffee daily, the mean endurance difference between caffeine and placebo was 34.8%, and for subjects drinking <6 cups it was 30.3%. There was no significant correlation between usual caffeine intake and endurance enhancement with caffeine ($P = 0.21$).

Treatment with caffeine also significantly increased the isometric submaximal strength with 54% (95% CI: 29–83, $P < 0.0001$) and reduced the perceived effort at 5 min cycling by 11% (95% CI: 5–17, $P = 0.002$), while postural stability in regard to measurement with eyes opened and closed was impaired by 25% (95% CI: 2–53, $P = 0.03$) and 43% (95% CI: 16–77, $P = 0.001$), respectively. For the measurement of postural stability with eyes opened, 21 of 30 subjects had an impaired stability with caffeine compared with placebo, and the same was true for 22 of 30 subjects in the postural stability test with eyes closed.

There were no indications of a significant effect of caffeine on perceived effort at exhaustion ($P = 0.21$), walking speed ($P = 0.40$), maximal muscular strength ($P = 0.26$), postural stability in the semitandem standing position ($P = 0.19$), and psychomotor function (reaction time: $P = 0.42$ and movement time: $P = 0.83$). The main results are shown in Table 2.

As for the secondary end points, there was no significant period effect or treatment \times period interaction for isometric arm flexion endurance ($P = 0.87$ and $P = 0.84$, respectively); perceived exertion during cycling ($P = 0.35$ and $P = 0.40$, respectively); movement time ($P = 0.06$ and $P = 0.42$, respectively); and postural stability with eyes opened ($P =$

0.17 and $P = 0.94$, respectively), with eyes closed ($P = 0.18$ and $P = 0.61$, respectively), and in the semitandem standing position ($P = 0.24$ and $P = 0.20$, respectively). However, although there was a statistically significant period effect for both reaction time ($P = 0.0007$) and walking speed ($P = 0.0006$), there was no indication of a period \times treatment interaction ($P = 0.93$ and $P = 0.17$, respectively). Of 30 subjects, 24 obtained their best reaction time and 23 obtained their best walking speed during period 2.

Withdrawal symptoms and side effects are summarized in Table 1. Withdrawal symptoms were generally present in both of the caffeine-fasting periods, whereas side effects were mainly present during the caffeine intervention period and lasted 1–3 h.

At the end of the study, participants were asked to estimate the order in which they had received caffeine and placebo, or to state if they detected no difference between the two capsules: 43% were unaware of any differences, 46% correctly guessed when they had received caffeine or placebo, and 11% guessed incorrectly.

DISCUSSION

In this study of healthy subjects aged ≥ 70 yr, caffeine treatment increased cycling endurance (by 25%) and isometric arm flexion endurance (by 54%) and reduced the perceived effort during cycling by 11%. Caffeine treatment also impaired the postural stability (by 25 and 45% with eyes opened and closed, respectively), but it had no significant effect on reaction and movement times. Following 48 h of caffeine withdrawal, one-half of the participants reported withdrawal symptoms. During treatment with caffeine, 40% of subjects noticed side effects (compared with 10% of subjects during placebo treatment).

This double-blind, placebo-controlled study was sufficiently powered to investigate different aspects of physical performance. At the end of the study, 43% of participants were unaware of any differences between the caffeine and placebo,

Table 2. Main results

	Placebo, median (95% CI for median)	Caffeine, median (95% CI for median)	Caffeine vs. Placebo	
			Mean difference (95% CI for mean)	<i>P</i> value
<i>Physical performance and perceived effort</i>				
Endurance, min	25.4 (14.7–30.6)	29.6 (21.7–41.6)	+25 (13–38)	0.0001
Perceived effort at 5 min, units	7 (6–9)	6 (6–7)	−11*(−17 to −5)	0.002
Perceived effort at exhaustion, units	12 (12–13)	12 (10–12)	−5*(−12–3)	0.21
Walking speed, s	8.2 (7.3–8.8)	8.0 (7.0–8.8)	−1 (−4–2)	0.40
Maximal muscular strength, N	479 (388–571)	459 (424–589)	+2 (−2–7)	0.26
Isometric submaximal strength, s	42.8 (34.7–47.6)	74.5 (51.1–86.4)	+54 (29–83)	<0.0001
<i>Psychomotor function</i>				
Reaction time, ms	485 (460–520)	489 (461–522)	+3 (−4–10)	0.42
Movement time, ms	254 (241–305)	272 (240–299)	−1 (−8–7)	0.83
<i>Postural sway</i>				
Velocity moment, EO, mm ² /s	8.6 (6.3–12.9)	10.2 (7.1–17.7)	+25† (2–53)	0.03
Velocity moment, EC, mm ² /s	16.1 (10.1–20.8)	22.2 (13.3–26.3)	+43† (16–77)	0.001
Velocity moment, semitandem, mm ² /s	41.2 (33.5–52.7)	48.7 (37.3–64.9)	+14† (−7–40)	0.19

CI, confidence interval; EO, eyes open; EC, eyes closed. *A negative result indicates less perceived effort at 5 min cycling for caffeine compared with placebo. †A positive result indicates an enhanced postural sway and thereby a reduced postural stability (balance) for caffeine compared with placebo.

46% correctly guessed when they had received caffeine or placebo, and 11% guessed incorrectly. This raises concern about the blinding of the participants; however, it is difficult to improve the blinding due to the increased number of side effects reported with caffeine compared with placebo (40 vs. 10%).

Several studies of younger individuals have found that caffeine increases endurance, e.g., in a crossover study by Graham and Spriet (15), 3 and 6 mg/kg caffeine increased endurance by 22% in well-trained athletes working at 85% of maximal oxygen consumption ($\dot{V}O_{2\max}$). Similarly, Greer et al. (17) showed an endurance increase by 26% in subjects cycling at 80% $\dot{V}O_{2\max}$ after ingestion of 6 mg/kg caffeine. Pasman et al. (33) also found that ingestion of 5 and 9 mg/kg of caffeine in well-trained athletes cycling to exhaustion at 80% $\dot{V}O_{2\max}$ increased endurance 23 and 26%, respectively. In younger subjects, the rate of perceived exertion has also been shown to be reduced by caffeine. Hence the effect of caffeine on endurance and rate of perceived effort seem to be quite similar in previous studies of younger subjects and in the present study of 75-yr-old participants. However, in our study, the working load was lower as subjects cycled at 65% of maximal heart rate corresponding to $\sim 55\%$ $\dot{V}O_{2\max}$, which should be below the threshold of lactate accumulation. The median perceived effort at exhaustion was also rather low: 12 units using Borg's 20-point scale. It would be expected that healthy elderly subjects are capable of working at higher loads for a prolonged period of time, as shown in a study by Overend et al. (30), where 12 men with a mean age of 70.7 yr worked 24 min on a cycle ergometer with a load of 115 W and a relative intensity of 91.5% $\dot{V}O_{2\max}$. The rather low rate of perceived exertion, together with a median working rate of 50 W and a low working intensity in relation to $\dot{V}O_{2\max}$, raises the question of what caused the participants to stop the endurance test? Was the increase in endurance with caffeine due to an increased ability to continue working, or was it rather a psychological effect of caffeine in way of reducing tiredness and increase alertness (20, 35)? The large interindividual variability in cycling endurance time could be due to the variation in habitual physical activity, ranging from 0 to 10 h weekly, or that the study group was allowed minor disabilities as hypertension and asthma.

The mechanism by which caffeine increases endurance is not fully understood. Caffeine elevates the muscular endurance in situations in which exhaustion is reached in the range of a few minutes to 2 h (11). In this range, sparing of glycogen is not likely the way by which caffeine induces this effect. The most widely supported theory is that caffeine acts by antagonism of the adenosine receptor (11, 13). Adenosine receptors are found in most tissues, including lipocytes and skeletal muscles (11), and activation of A_1 receptors leads to inhibition of lipolysis, activation of potassium channels, reduction in the atrioventricular node conduction, and inhibition of the basal and provoked neuronal activity (29). As caffeine acts as an adenosine-receptor antagonist, caffeine ingestion can thereby lead to elevation of free fatty acids before and during exercise (5, 15), decrease the extracellular potassium concentration and by this promote action potential in muscle cells (4, 26, 29), and provoke release of the neurotransmitter serotonin that has a possible effect in mediating the feeling of fatigue (28, 32). Caffeine is also associated with elevated plasma epinephrine,

and glycogen sparing does occur in the active muscle, at least in the first few minutes (13). Cortisol release is often associated with the stress originating from physical work (3), and caffeine ingestion significantly increases plasma cortisol (25, 27).

As most subjects in this study were habitual caffeine users with a mean daily intake of approximately five cups of coffee, the withdrawal from caffeinated drinks and food 48 h before session, combined with a single dose of 6 mg/kg caffeine, could be thought to influence the improvement in endurance time, but we found no correlation between usual coffee intake and endurance enhancement with caffeine ($P = 0.21$).

The 54% increase in isometric arm flexion endurance is somewhat greater than the 17% reported in an earlier study (34). Although the exact cause of this difference is unknown, the subjects in the previous study were ~ 23 yr old and performed repeated quadriceps contractions. By comparison, this study tested the isometric endurance of subjects aged ≥ 70 yr, generating a constant force corresponding to 50% of their maximal arm flexion strength. Similar to findings in studies of younger persons (19, 43), caffeine had no effect on maximal voluntary strength. The reported effect of caffeine on psychomotor function is somewhat conflicting (21, 24, 35), but, in this study, there was no indication that caffeine improved either reaction or movement times. The frequency of withdrawal symptoms (20, 22, 40) and side effects (21, 24) associated with caffeine, as well as the impaired postural stability (10, 41), are in accordance with previous findings. Thus in one study by Franks et al. (10), body sway was significantly increased in the young subjects 40 min after ingesting 4.3 mg/kg caffeine, and also elderly subjects in a study by Swift and Tiplady (41) showed an increased body sway on caffeine compared with placebo. In this study, postural stability was impaired by 25 and 45% with eyes opened and closed, respectively. The mechanism by which caffeine could influence postural stability is also most likely by antagonism of the adenosine receptors in the central nerve system, as blockade of these receptors leads to removal of the inhibitory effect by adenosine and thereby release of neurotransmitters as dopamine, which has been closely coupled to physical performance and has an important role in controlling the locomotor function (39).

All in all, caffeine is a very active drug that elicits many effects on humans, including the increase in exercise endurance, and this effect is probably due to a mixture of the different mechanisms above. The endurance-enhancing effects of caffeine may be useful in relation to the increase in the number of elderly with an active physical lifestyle or for improving physical training response through an exercise or rehabilitation program, although care should be taken with the use of caffeine treatment in the elderly population due to the effect of caffeine on the cardiovascular system, leading to a rise in blood pressure and pulse (36). Care should also be taken as caffeine ingestion leads to a reduction in insulin-mediated glucose uptake due to insulin resistance (14, 23), possibly mediated by elevated epinephrine (42). High doses of caffeine can lead to "caffeinism" with polyuria, trembling, dizziness, irregular pulse and ventilation, abdominal discomfort, and diarrhea (16), some of the symptoms, although less intensive, that were reported in 40% of subjects in the study, so side effects, together with the impairment of postural stability, may limit the use of caffeine in the elderly.

An earlier study indicated that coffee may contain components that block the endurance effect of caffeine (12). Consequently, this study examined the effect of caffeine in individuals who abstained from caffeine 48 h before each session, and, in relation to possible use in the elderly population, it is important to determine whether a shorter period of caffeine withdrawal would be sufficient. In conclusion, more studies are required to determine the clinical usefulness of the endurance-enhancing effect of caffeine ingestion.

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